ADH1B VIP Summary

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Authors: Michelle Whirl-Carrillo

Background

Alcohol dehydrogenases metabolize ethanol to acetaldehyde, which is subsequently metabolized by aldehyde dehydrogenases (ALDH1A, ALDH2 genes) to acetate. This metabolism occurs primarily in the liver [Article:14693654]. The Class I alcohol dehydrogenase family is comprised of ADH1A, ADH1B and ADH1C. Collectively, the Class I ADHs are responsible for the metabolism of about 70% of ethanol in the liver at a concentration of approximately 22mM [Article:16571603]. The Class I ADHs are very similar genes; each is approximately 15 kb in size, and the resulting proteins share a 93% amino acid sequence identity [Article:11274460]. All three Class I genes are clustered on chromosome 4, specifically in the region 4q22 [Articles:15099407, 16571603]. This class of ADHs is inhibited by pyrazole and its derivatives [Article:15099407].

ADH1B Protein

ADH1B is expressed predominantly in the liver [Article:16792560]. The Km and Vmax values for ethanol as a substrate for ADH1B vary widely depending on the allele of ADH1B, with the *1 allele displaying the lowest Km and Vmax [Article:15099407]. The ADH1B*1 protein structure has been elucidated by x-ray crystallography, and a binding site has been localized near the zinc atom. The ADH1B*1 binding site is predicted to be more restrictive than either ADH1A or ADH1C*2 [Article:11274460]. In vivo, ADH1B exists as a dimer [Article:10441588]. It can either form homodimers or heterodimers with other class 1 ADHs [Article:15099407].

ADH1B Variation

ADH1B*2 and ADH1C*1 are responsible for a more rapid metabolism of alcohol than the other ADH1B and ADH1C alleles. There are conflicting studies as to whether these alleles are in linkage disequilibrium [Article:10441588]. A study of three different Taiwanese populations found the genes to be in linkage disequilibrium [Article:10090900], and LD has also been found in several Caucasian populations [Article:14693654]. However, in other studies, the effect of ADH1C*1 is independent of the ADH1B*2 allele. One study analyzing the drinking habits of Japanese men found this to be the case [Article:17285601]. Another study focusing on a population from Trinidad and Tobago also found independence between ADH1B and ADH1C [Article:17134660].

ADH1B and Disease Associations

ADH1B has been studied with conflicting results in association with Fetal Alcohol Syndrome, oral cancer, esophageal cancer, colorectal cancer, testicular atrophy and breast cancer [Article:15099407]. ADH1B genotype has been linked to esophageal cancer along with ALDH2 [Article:17036331]. In another study, ADH1B genotype did not correlate with the risk of laryngeal cancer in a population of Caucasian Germans [Article:12668919]. In yet another study, no correlation was found between ADH1B or ADH1C genotype and alcoholism or liver disease in a Spanish male population [Article:15519646].

ADH1B has been thought to be secondary in importance to ALDH2 in the metabolic conversion of ethanol to acetate. However, at least two studies suggest that protection from alcoholism may affected by ADH1B independently of ALDH2 [Articles:10441588, 16086315].

The ADH1B*1 allele has been shown to correlate with increased risk of colorectal cancer in one study [Article:17517051]. It has also been associated with increased risk of squamous cell cancer of the head and neck (SCCHN) [Article:17489985]. In one study, the ADH1B*1 allele correlated with the risk of cerebral infarction in Japanese men [Article:15534263]. This allele is more common in alcoholics and in heavy drinkers than in moderate drinkers [Article:15099407]. It is the most prevalent allele in Caucasians, although ADH1B*2 is also found in that population. It is rarely found in Asian populations.

Important Variant: ADH1B*2 (rs1229984)

ADH1B*2 (Arg47His in exon 3) has been shown in vitro to metabolize ethanol to acetaldehyde more quickly than the *1 allele. [Article:17295732]. It has a Vmax about 40 times that of the *1 allele [Article:16571603]. This allele has been repeatedly reported to protect against alcoholism or alcohol use disorders (AUD) due to increased sensitivity to alcohol. The higher levels of accumulated acetaldehyde seem to be responsible for uncomfortable symptoms such as flushing, headaches, nausea that carriers of the *2 allele experience (especially homozygotes) [Article:10441588].

The ADH1B*2 allele is the predominant allele in Asian populations [Article:10441588]. Within Asians, the *2 allele was more common among non-alcoholics than alcoholics, with similar findings in other populations. [Article:15099407]. However there are indications that if those with the *2 genotype continue to drink in spite of the adverse reactions, they could be at risk for liver damage due to increased levels of acetaldehyde [Article:15099407]. But no conclusive evidence of liver disease and ADH genotype has been found to date [Article:16792560].

Note: The *ADH1B* gene is found on the minus chromosomal strand. Please note that for standardization, the PharmGKB presents all allele base pairs on the positive chromosomal strand, therefore the alleles within our variant annotations will differ (in a complementary

manner) from those in this VIP summary that are given on the minus strand as reported in the literature.

Important Variant: ADH1B*3 (rs2066702)

ADH1B*3 (Arg369Cys in exon 9) has been found in some African American and Native American populations to be correlated with protection against alcoholism [Articles:17718395, 17718396, 16571603]. It has a Vmax about 30 times higher than the *1 allele [Article:16571603]. This allele is not typically found in the Asian or Caucasian populations.

Note: The *ADH1B* gene is found on the minus chromosomal strand. Please note that for standardization, the PharmGKB presents all allele base pairs on the positive chromosomal strand, therefore the alleles within our variant annotations will differ (in a complementary manner) from those in this VIP summary that are given on the minus strand as reported in the literature.